Design and synthesis of a bis(hydroxyphenyl)diamide bearing a pendant thiazolium unit; application to the catalytic asymmetric intramolecular Stetter reaction

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Abstracts

The bis(hydroxyphenyl)diamide architecture constitutes as a privileged ligand that promotes a number of catalytic asymmetric transformations in combination with rare-earth metals. A new diamide analogue armed with a carbene catalytic function derived from a thiazolium unit was designed, synthesized, and applied to the catalytic asymmetric intramolecular Stetter reaction. Cooperative work between the carbene function and hydrogen bonding interactions was suggested to give the enantioenriched chroman derivatives.

1. Introduction

The concept of cooperative catalysis has gained in popularity in the chemical community as a robust strategy with which to catalyze a number of transformations.¹ The key feature of this approach is the simultaneous activation of multiple substrates and/or functional groups through multiple catalytic functions, rendering a specific reaction promoted under mild conditions. Inspired by the catalytic system of metalloenzymes that uses Lewis acidic or redox active metals and a peripheral peptide to activate and control the stereochemical course of a reaction through hydrogen bonding interactions, we have developed a catalytic system based on amide-based ligand **1**, incorporating a rare-earth metal. This structurally flexible ligand serves as a small-fragment peptide that forms an associative complex with a rare-earth metal and the substrate(s) at the transition state through metal coordination and hydrogen bonding.²⁻⁴ The bis(hydroxyphenyl)diamide architecture of **1** serves as a privileged ligand in combination with rare-earth metals; a marginal difference in the ionic radius of the rare-earth metals was leveraged by the conformational flexibility of **1**, indicating that the **1**/rare-earth metal catalytic system could encompass a wide range of catalytic asymmetric transformations e.g. amination,⁵ hydroxylation,⁶ Mannich-type reactions,⁷ and conjugate addition reactions (Figure 1).⁸ The collected examples indicate that the Lewis acid function of a rare-earth metal and hydrogen bonding through the amide and hydroxyl groups are key to achieving efficient catalysis with stereochemical control. The utility of this catalytic system was further broadened by the tactical use of an alkali metal to produce a series of bimetallic catalysts for nitroaldol reactions,⁹ nitro-Mannich reactions,¹⁰ and Conia-ene reactions.¹¹ In these studies, valine or leucine was used as an α -amino acid for the synthesis of **1**, and the primary role of the residue part (R) was

simply as a stereochemical descriptor. Given the broad utility of **1** in asymmetric catalysis,^{2,5–11} we reasoned that the installation of a catalytic function in this molecule would open up a new avenue in catalysis. We focused on the installation of a carbene group as a catalytic functionality because a carbene provides a rich chemistry in catalysis and is orthogonal to both the hard Lewis acid function and to hydrogen bonding interactions.¹² Herein we document the synthesis of a bis(hydroxyphenyl)diamide bearing a pendant thiazole-based carbene and detail its application in catalytic asymmetric intramolecular Stetter reactions.

Figure 1. The structure of the prototype ligand **1** and an advanced ligand armed with a carbene functional group.

2. Results and discussion

The synthesis of bis(2-hydroxyphenyl)diamide **2** bearing a thiazolium ring started with the amide coupling of Boc-protected L-thiazolylalanine **3** and 2-benzyloxylaniline (Scheme 1).¹³ For the formation of the analogous amide linkage for nonfunctionalized α -amino acids, e.g. Boc-valine and Boc-leucine, pivaloyl chloride was used as a cost-effective reagent to produce a mixed anhydride as a reactive

intermediate. However, in contrast to the successful amide formation for those amino acids,

Scheme 1. Synthesis of enantiomerically pure bis(2-hydroxyphenyl)diamide **1** bearing a thiazolium group.

application of the same reaction conditions to **3** resulted in a decrease in the enantiopurity, giving amide **4** with 77% ee (Scheme 2). The employment of commonly used coupling reagents e.g. EDCI/HOBt also resulted in partial racemization, presumably because the neighboring nitrogen on the thiazole ring facilitated racemization *via* the intermediary activated lactam **A**.¹⁴ We were pleased to identify racemization-free conditions when isobutyl chloroformate and *N*-methylmorpholine were employed at -15 °C, and the subsequent addition of 2-benzyloxyaniline afforded amide **4** in enantiomerically pure form without chromatographic purification.¹⁵ The crude material obtained from the coupling reaction was reacted directly with 4M HCl/CPME (cyclopentyl methyl ether) in CH₂Cl₂ to give amine hydrochloric salt **5** in 94% yield over two steps, without chromatographic purification. The formation of the

first report on the catalytic asymmetric intramolecular Stetter reaction by Enders,^{17,18} several catalytic systems have been developed to furnish enantioenriched cyclic 1,4-dicarbonyl entities.¹⁹

Screening of the reaction conditions was performed using substrate **8a**, which was expected to provide enantioenriched chroman derivative **9a** (Table 1). Initial attempts to perform the reaction using **2a–c** with KHMDS as a base in dioxane produced promising enantioselectivity (entries 1–3). Compound **2c** afforded the highest enantioselectivity, whereas **2a** and **2b** gave better yields. In contrast to soluble **2c**, compounds **2a** and **2b** were insoluble in common organic solvents even after carbene formation with base. Considering that homogeneous reaction mixtures are generally more reliable and advantageous to obtain reproducibility, compound **2c** was used in further screening. The use of more polar or less polar aprotic solvents barely gave the desired product **9a**, while lower enantioselectivity was also observed (entries 4–7). The use of MeOH as a protic polar solvent gave **9a** in high yield, albeit with no enantioselectivity; this was likely due to the absence of the stereodifferentiation caused by disruption of the hydrogen bonding interactions (entry 8).²⁰ Other inorganic and amine bases were examined, but only marginal differences in the reaction outcome were observed (entries 9–11). For ease of handling, availability, and a higher yield, one equivalent of NaOAc was adopted for further optimization (entry 12). The high levels of conversion observed in MeOH implied that a proton source facilitated the reaction, leading us to examine protic additives.²¹ The use of a cosolvent system of dioxane and MeOH improved the yield, but led to a reduction in enantioselectivity (entry 13). Phenolic additives accelerated the reaction while maintaining the enantioselectivity, and the best performance was observed with *p*-methoxyphenol (entries 14–16). Higher

reaction temperatures led to higher conversion at the expense of lower enantioselectivity (Table 1, entry 17). The use of a catalytic amount (10 mol%) of rare-earth metal nitrates as Lewis

Table 1. Catalytic asymmetric intramolecular Stetter reaction catalyzed by bis(2-hydroxyphenyl)diamide **2** bearing a thiazolium unit.^a

Entry	2	base	x	additive	y	solvent	Temp (°C)	Yield ^b (%)	Ee ^c (%)
1	2a	KHMDS	20			dioxane	rt	32	64
2	2b	KHMDS	20			dioxane	rt	62	53
3	2c	KHMDS	20			dioxane	rt	21	67
4	2c	KHMDS	20			CH ₂ Cl ₂	rt	trace	34
5	2c	KHMDS	20			THF	rt	trace	53
6	2c	KHMDS	20			EtOAc	rt	trace	49
7	2c	KHMDS	20			CH ₃ CN	rt	<10	36
8	2c	KHMDS	20			MeOH	rt	90	0
9	2c	KO ^t Bu	20			dioxane	rt	22	68
10	2c	DBU	20			dioxane	rt	trace	70
11	2c	NaOAc	40			dioxane	rt	20	71
12	2c	NaOAc	100			dioxane	rt	28	64
13	2c	NaOAc	100	MeOH ^d		dioxane	rt	92	4
14	2c	NaOAc	100	catechol	100	dioxane	rt	41	56
15	2c	NaOAc	100	2,6-(^t Bu)-C ₆ H ₄ OH	100	dioxane	rt	36	67
16	2c	NaOAc	100	4-MeO-C ₆ H ₄ OH	100	dioxane	rt	52	63
17	2c	NaOAc	100	4-MeO-C ₆ H ₄ OH	100	dioxane	60	93	33
18	2c	NaOAc	100	La(NO ₃) ₃ ·6H ₂ O	10	dioxane	rt	44	54
19	2c	NaOAc	100	Nd(NO ₃) ₃ ·6H ₂ O	10	dioxane	rt	52	58
20	Bn ₂ - 2c ^e	NaOAc	100	4-MeO-C ₆ H ₄ OH	100	dioxane	rt	80	34

^a 0.1 mmol of **8a** was used.

^b Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture with 1,1,2,2-tetrachloroethane as an internal standard.

^c Determined by HPLC analysis.

^d Dioxane/MeOH (1:1) was used as the solvent.

^e **7c** was used instead of **2c**.

acidic additives was also beneficial, and the reaction gave higher conversion, although it was less effective than that with *p*-methoxyphenol as an additive (entries 18 and 19). The reaction using **7c** (i.e., bis-benzyl protected **2c**) under otherwise identical conditions to those described in entry 16 resulted in higher conversion with lower enantioselectivity, suggesting that the two phenolic hydroxyl groups of **2c** might participate in stereo differentiation and partially disturb the reaction (entry 20).

The substrate scope of the reaction was then investigated under the optimum conditions (Table 1, entry 16). The ester moiety was found to influence the enantioselectivity, while the ^tBu ester was more suitable for the present catalytic system (Table 2, entries 1 and 2). Substrates bearing electron-donating substituents on the aromatic ring led to similar levels of reactivity and enantioselectivity (entries 3 and 4). In contrast, chloro-substituted substrate **8e** showed a different behavior, giving **9e** in higher yield but with lower enantioselectivity (entry 5). When **9e** was subjected to the catalytic conditions, gradual racemization was revealed, which became more prominent over longer reaction times, thus suggesting that racemization occurred through partial enolization due to the higher acidity of α -proton of **9e** (Scheme 3). Compound **8e** was inherently reactive; therefore the reaction conditions were modified slightly with a reduced amount of base (15 mol%), and *p*-methoxyphenol was omitted; these changes led to a reaction outcome that was comparable to that observed for **9a–d** (entry 6). Substrate **8f** bearing an electron-withdrawing ethoxycarbonyl group showed a similar

tendency and a longer reaction time gave the product with lower enantioselectivity.²²

The application of a substrate bearing an α,β -unsaturated nitrile moiety produced racemic product **9g**, implying that a hydrogen bond to the ester moiety played a crucial role in the stereodifferentiation (entry 8).

Table 2. Substrate scope of the catalytic asymmetric intramolecular Stetter reaction.^a

2c

20 mol%

NaOAc 1 equiv
4-MeO-C₆H₄OH 1 equiv

dioxane, rt

R = CH₂C₆H₄-*p*-OⁿC₁₀H₂₁

8 → **9**

Entry	substrate 8		product	Time (h)	Yield ^b (%)	Ee ^c (%)	
	R ¹	R ²					
1	H	CO ₂ ^t Bu	8a	9a	48	53	62
2	H	CO ₂ Et	8b	9b	48	50	50
3	Me	CO ₂ ^t Bu	8c	9c	48	45	63
4	MeO	CO ₂ ^t Bu	8d	9d	48	60	59
5	Cl	CO ₂ ^t Bu	8e	9e	48	88	38
6 ^d	Cl	CO ₂ ^t Bu	8e	9e	21	50	59
7	EtO ₂ C	CO ₂ ^t Bu	8f	9f	24	54	55
8	H	CN	8g	9g	48	66	0

^a 0.3 mmol of **8** was used.

^b Isolated yield.

^c Determined by HPLC analysis.

^d The reaction was run with 15 mol% NaOAc in the absence of *p*-methoxyphenol.

Scheme 3. Partial racemization of **9e** under the reaction conditions.

3. Conclusion

In conclusion, the bis(hydroxyphenyl)diamide ligand has been advanced with the installation of a catalytic functionality, namely a thiazolium unit. Partial racemization was associated with amide coupling depending on the conditions. The diamide was evaluated in the catalytic asymmetric intramolecular Stetter reaction, and both the thiazolium carbene function and hydrogen bond interactions led to enantioenriched products. Although the enantioselectivity remains unsatisfactory, the diamide bearing the thiazolium unit is anticipated to serve as an archetypal ligand for cooperative catalysis with the carbene function. Further application to enantioselective reactions including those promoted by transition metal carbene complexes will be reported in due course.

4. Experimental

General

The catalytic asymmetric Stetter reaction was performed in a 20 mL glass test tube with a 3-way glass stopcock under an Ar atmosphere unless otherwise noted. Air- and moisture-sensitive liquids were transferred *via* a gas-tight syringe and a stainless-steel needle. All work-up and purification procedures were carried out with reagent-grade solvents under an ambient atmosphere. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR was recorded on JEOL ECS-400 or ECS-600. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CDCl₃: δ 7.24 ppm, CD₃OD: δ 3.31 ppm). For ¹³C NMR, chemical shifts are reported in the scale relative to NMR solvent (CDCl₃: δ 77.0 ppm, CD₃OD: δ 49.0 ppm)

as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotations were measured using a 2 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High resolution mass spectra (ESI Orbitrap (+)) were measured on ThermoFisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (0.46 cm ϕ x 25 cm).

4.1 Catalytic asymmetric intramolecular Stetter reaction.

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with thiazolium salt **2c** (20 mol%) and substrate **8** (0.3 mmol, 1 eq.). To this test tube were added NaOAc (24.6 mg, 0.3 mmol, 1 eq.) and *p*-methoxyphenol (37.2 mg, 0.3 mmol, 1 eq.) in a dry box under an Ar atmosphere. After placing under vacuum for 1 h, anhydrous 1,4-dioxane (1.5 mL, 0.2 M) was added. The resulting solution was allowed to stir at ambient temperature for 48 h. The reaction mixture was then loaded directly onto a silica gel column, eluted with a suitable solution of *n*-hexane and ethyl acetate (typically 10:1). Evaporation of the solvent afforded the analytically pure desired product. Compounds **9a**, **9b**, **9c**, **9d** and **9g** are known compounds. CAS numbers: **9a**: 845749-05-5; **9b**: 1046825-09-5; **9c**: 845749-07-7; **9d**: 845749-09-9; **9g**: 193806-89-2.

4.1.1 (*R*)-*tert*-Butyl 2-(4-oxochroman-3-yl)acetate **9a**

$[\alpha]_{\text{D}}^{27} = -2.3$ (*c* 1.8, CHCl₃, 62% ee); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-popropanol/*n*-hexane = 1/10, flow rate 1.0 mL/min,

detection at 254 nm, t_R = 11.8 min (major), 12.6 min (minor)).

4.1.2. (*R*)-Ethyl 2-(4-oxochroman-3-yl)acetate **9b**

$[\alpha]_D^{27} = -2.5$ (c 1.7, CHCl_3 , 50% ee); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/10, flow rate 1.0 mL/min, detection at 254 nm, t_R = 15.7 min (major), 19.9 min (minor)).

4.1.3. (*R*)-*tert*-Butyl 2-(6-methyl-4-oxochroman-3-yl)acetate **9c**

$[\alpha]_D^{27} = -6.6$ (c 1.7, CHCl_3 , 63% ee); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/10, flow rate 1.0 mL/min, detection at 254 nm, t_R = 11.2 min (major), 12.0 min (minor)).

4.1.4. (*R*)-*tert*-Butyl 2-(6-methoxy-4-oxochroman-3-yl)acetate **9d**

$[\alpha]_D^{27} = -12.7$ (c 2.3, CHCl_3 , 59% ee); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/10, flow rate 1.0 mL/min, detection at 254 nm, t_R = 13.6 min (major), 14.2 (minor)).

4.1.5. (*R*)-*tert*-Butyl 2-(6-chloro-4-oxochroman-3-yl)acetate **9e**

Viscous liquid: R_f = 0.5 (4:1 *n*-hexane to ethyl acetate); IR (CHCl_3 solution) ν 2982, 1724, 1697, 1605, 1477, 1279, 1153, 1022, 826, 670 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.82 (s, 1H), 7.40–7.38 (m, 1H), 6.10 (d, J = 8.9 Hz, 1H), 4.56 (dd, J = 5.2, 11.0 Hz, 1H), 4.27 (t, J = 12.0 Hz, 1H), 3.25–3.22 (m, 1H), 2.79 (dd, J = 4.8, 16.8 Hz, 1H), 2.34 (dd, J = 8.2, 16.8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.6, 170.2,

160.1, 135.7, 127.0, 126.6, 121.3, 119.5, 81.3, 70.4, 42.4, 31.4, 28.0; HRMS (ESI) Anal. calcd. for $C_{15}H_{17}N_3O_4ClNa$ m/z 319.0708 $[M+Na]^+$, found 319.0714; $[\alpha]_D^{27} = -0.4$ (c 1.5, $CHCl_3$, 59% ee); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-propanol/ n -hexane = 1/10, flow rate 1.0 mL/min, detection at 254 nm, t_R = 25.4 min (major), 26.4 min (minor)).

4.1.6. (*R*)-Ethyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-4-oxochroman-6-carboxylate 9f

Viscous liquid: R_f = 0.4 (4:1 n -hexane to ethyl acetate); IR ($CHCl_3$ solution) ν 3406, 3020, 1708, 1614, 1418, 1364, 1022, 666 cm^{-1} ; ^1H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J = 2.1 Hz, 1H), 8.12 (dd, J = 2.1, 8.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 1H), 4.63 (dd, J = 5.5, 11.4 Hz, 1H), 4.36–4.30 (m, 3H), 3.32–3.24 (m, 1H), 2.83 (dd, J = 4.8, 17.0 Hz, 1H), 2.35 (dd, J = 8.0, 17.0 Hz, 1H), 1.45 (s, 9H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.0, 170.3, 165.5, 164.7, 136.8, 136.6, 129.8, 129.6, 124.0, 123.9, 120.0, 118.3, 81.4, 70.4, 61.3, 42.4, 31.4, 28.2, 27.9, 14.4; HRMS (ESI) Anal. calcd. for $C_{18}H_{22}O_6Na$ m/z 357.1309 $[M+Na]^+$, found 357.1306; $[\alpha]_D^{27} = -5.6$ (c 1.9, $CHCl_3$, 55% ee sample); HPLC analysis (CHIRALPAK IA (ϕ 0.46 cm x 25 cm) and IA-3 (ϕ 0.46 cm x 25 cm), 2-propanol/ n -hexane = 1/10, flow rate 1.0 mL/min, detection at 254 nm, t_R = 17.2 min (minor), 19.4 min (major).

4.2. Synthesis of compound 2

4.2.1 (*S*)-*tert*-Butyl (1-((2-(benzyloxy)phenyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-yl)carbamate 4

At first, 272 mg of L-thiazolylalanine (1 mmol, 1 eq.) were dissolved in dry DCM (10

mL, 0.1 M), and cooled to $-15\text{ }^{\circ}\text{C}$ for 10 min. To this solution, NMM (110 μL , 1 mmol, 1 eq.) was added, followed by the dropwise addition of isobutyl chloroformate (132 μL , 1.02 mmol, 1.02 eq.). A white crystalline solid was immediately formed. After stirring at this temperature for 0.5 h, pre-cooled 2-(benzyloxy)aniline in 5 mL of dry DCM (199 mg, 1 mmol, 1 eq.) was slowly added *via* cannula. The reaction mixture was stirred for 0.5 h at $-15\text{ }^{\circ}\text{C}$, then gradually warmed to room temperature. After the disappearance of the starting material, the volatiles were removed under reduced pressure. For confirmation of enantiopurity by HPLC, a small aliquot of the crude material was purified by flash column chromatography. For further synthesis, the concentrated mixture was re-dissolved in THF. Filtration and evaporation gave a light green viscous liquid, which was used directly in the next step, i.e., the deprotection of the Boc group.

White solid: $R_f = 0.5$ (1:1 *n*-hexane to ethyl acetate); m.p. $125\text{--}126\text{ }^{\circ}\text{C}$; IR (CHCl_3 solution) ν_{max} 3020, 3012, 1710, 1600, 1535, 1363, 1221, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (br, 1H), 8.39 (s, 1H), 8.31 (dd, $J = 1.6, 7.8\text{ Hz}$, 1H), 7.44–7.33 (m, 5H), 7.04 (s, 1H), 6.99–6.86 (m, 3H), 6.26 (br, 1H), 5.06 (d, $J = 11.9\text{ Hz}$, 1H), 5.02 (d, $J = 11.9\text{ Hz}$, 1H), 4.67 (br, 1H), 3.43 (br, 1H), 3.24 (dd, $J = 5.5, 14.7\text{ Hz}$, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 155.6, 152.9, 152.8, 147.2, 136.5, 128.7, 128.2, 127.5, 127.2, 123.9, 121.3, 119.9, 115.7, 111.6, 80.1, 70.5, 55.3, 33.1, 28.2; HRMS (ESI) Anal. calcd. for $\text{C}_{24}\text{H}_{28}\text{O}_4\text{N}_3\text{S}$ m/z 454.1795 $[\text{M}+\text{H}]^+$, found 454.1785, $\text{C}_{24}\text{H}_{27}\text{O}_4\text{N}_3\text{NaS}$ m/z 476.1614 $[\text{M}+\text{Na}]^+$, found 476.1600; $[\alpha]_{\text{D}}^{27} = -6.6$ (c 0.7, CHCl_3); HPLC analysis (CHIRALPAK IC (ϕ 0.46 cm x 25 cm), ethanol/*n*-hexane/triethylamine = 30/70/0.1, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 8.8\text{ min}$ (major).

4.2.2. (S)-1-((2-(Benzyloxy)phenyl)amino)-1-oxo-3-(thiazol-4-yl)

propan-2-aminium chloride **5**

The crude **4** in the previous step was dissolved in DCM. After cooling to 0 °C for 10 min, 4M HCl in CPME (2 mL) was added slowly. After 0.5 h at 0 °C, the reaction was returned to room temperature. A white solid gradually precipitated from the solution until no starting material was detected by TLC in the solution (around 2 h). To this solution, an excess amount of diethyl ether was added. Filtration and washing with diethyl ether gave **5** as a white solid (366 mg, 94% yield in two steps): $R_f = 0.3$ (15:1 dichloromethane to methanol); m.p. 123–125 °C; IR (CH₃OH solution) ν 3582, 3294, 1669, 1536, 744 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.82 (d, $J = 1.8$ Hz, 1H), 8.21–8.18 (m, 1H), 7.44–7.42 (m, 2H), 7.35–7.23 (m, 4H), 7.01–6.98 (m, 2H), 6.91–6.87 (m, 1H), 5.06 (s, 2H), 3.82 (dd, $J = 3.6, 8.2$ Hz, 1H), 3.32 (dd, $J = 4.1, 14.4$ Hz, 1H), 3.03 (dd, $J = 8.2, 14.4$ Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 174.7, 155.5, 154.9, 149.6, 138.2, 129.5, 128.9, 128.5, 128.4, 125.6, 122.0, 121.4, 117.0, 113.4, 71.4, 56.8, 36.8; HRMS (ESI) Anal. calcd. for C₁₉H₂₀O₂N₃S⁺ m/z 354.1271 [M–Cl]⁺, found 354.1297. $[\alpha]_D^{27} = -17.9$ (c 0.5, CH₃OH).

4.2.3. (S)-2-(Benzyloxy)-N-(1-((2-(benzyloxy)phenyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-yl)benzamide **6**

At first, compound **5** (15 mg, 0.5 mmol, 1 eq.) was suspended in dry DCM (10 mL). To this mixture, Et₃N (174 μ L, 1.25 mmol, 2.5 eq.) was added. After cooling at 0 °C for 10 min, pre-cooled 2-(benzyloxy)benzoyl chloride (148 mg, 0.6 mmol, 1.2 eq.) in 2 mL of DCM was added slowly. The reaction mixture was stirred at this temperature for 0.5 h, then gradually warmed to room temperature. After removal of volatiles under reduced pressure, column chromatography with *n*-hexane/ethyl acetate (25% ethyl acetate) gave **6** as a white solid (231 mg, 82%): *R_f* = 0.4 (1:1 *n*-hexane to ethyl acetate); m.p. 76–77 °C; IR (CHCl₃ solution) ν 3482, 3219, 2032, 1689, 1548, 1041, 806 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.92 (d, *J* = 9.4 Hz, 2H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.25 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.42–7.33 (m, 2 H), 7.28–7.24 (m, 6H), 7.18–7.12 (m, 3H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.99–6.91 (m, 3H), 6.87–6.84 (m, 2H), 5.26 (dd, *J* = 6.0, 12.2 Hz, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 5.04 (d, *J* = 11.6 Hz, 1H), 5.00 (d, *J* = 11.6 Hz, 1H), 4.96 (d, *J* = 11.6, 1H), 3.32 (dd, *J* = 6.0, 14.9 Hz, 1H), 3.24 (dd, *J* = 5.5, 14.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 165.5, 156.9, 153.0, 152.4, 147.2, 136.2, 135.6, 133.0, 132.4, 128.7, 128.40, 128.37, 127.9, 127.7, 127.4, 127.2, 123.7, 121.3, 121.2, 120.0, 115.1, 112.8, 111.4, 70.9, 70.4, 54.0, 32.6; HRMS (ESI) Anal. calcd. for C₃₃H₃₀O₄N₃S *m/z* 564.1952 [M+H]⁺, found 564.1944; C₃₃H₂₉O₄N₃NaS *m/z* 586.1771 [M+Na]⁺, found 586.1758; [α]_D²⁷ = +48.7 (*c* 0.5, CHCl₃); HPLC analysis (CHIRALPAK IC (ϕ 0.46 cm x 25 cm), ethanol/*n*-hexane/triethylamine = 30/70/0.1, flow rate 1.0 mL/min,

detection at 254 nm, t_R = 24.5 min (major).

4.2.4. (S)-4-(2-(2-(Benzyloxy)benzamido)-3-((2-(benzyloxy)phenyl)amino)-3-oxopropyl)-3-methylthiazol-3-ium iodide 7a

At first, compound **6** (113 mg, 0.2 mmol, 1 eq.) was dissolved in DMF (0.2 mL, 1 M). To this solution, CH₃I (2 mL) was added. The reaction was monitored by TLC until **6** was consumed (typically 2 days). The excess CH₃I was evaporated off and the reaction mixture was loaded directly onto column chromatography with a gradient elution of DCM/CH₃OH (0–5% CH₃OH). Evaporation of the solvent and trituration with diethyl ether afforded **7a** as a light yellow solid (135 mg, 96% yield): R_f = 0.3–0.5 (7:1 dichloromethane to methanol); m.p. 107–109 °C; IR (CH₃OH solution) ν 3591, 3189, 2169, 1659, 1121, 814 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.68 (s, 1H), 8.90 (s, 1H), 8.63 (d, J = 8.0 Hz, 1H), 8.08–8.04 (m, 1H), 7.98 (dd, J = 1.6, 7.8 Hz, 1H), 7.47–7.43 (m, 2H), 7.37–7.30 (m, 4H), 7.26–7.24 (m, 3H), 7.16–7.10 (m, 3H), 7.07–6.98 (m, 3H), 6.95–6.91 (m, 2H), 5.38 (t, J = 6.6 Hz, 1H), 5.17–4.99 (m, 4H), 4.21 (s, 3H), 3.30 (dd, J = 6.4, 16.0 Hz, 1H), 3.08 (dd, J = 7.4, 15.8 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 169.4, 168.1, 158.2, 150.5, 147.5, 137.9, 137.2, 134.8, 132.2, 129.8, 129.54, 129.48, 129.3, 129.0, 128.6, 127.6, 126.8, 123.9, 123.5, 122.3, 122.2, 121.9, 114.6, 113.6, 72.1, 71.4, 53.1, 41.0, 30.6; HRMS (ESI) Anal. calcd. for C₃₄H₃₂O₄N₃S⁺ m/z 578.2108 [M–I]⁺, found 578.2098; $[\alpha]_D^{27}$ =

–10.8 (*c* 1.4, CH₃OH).

4.2.5. (S)-4-(2-((-hydroxybenzamido)-3-((2-hydroxyphenyl)amino)-3-oxopropyl)-3-methylthiazol-3-ium iodide 2a

At first, compound **7a** (71 mg, 0.1 mmol, 1 eq.) was dissolved in dry DCM (1 mL), and cooled to –78 °C for 0.5 h. After complete cooling, BBr₃ (1 mL, 1 M in DCM, 1 mmol, 5 eq. to Bn group) was added very slowly to the avoid temperature increasing. The reaction mixture was allowed to stir at –78 °C for another 0.5 h, after which 1 mL of isopropanol was added to quench the reaction at –78 °C. The mixture was stirred for 10 min at –78 °C, and then warmed to 0 °C. Excess diethyl ether was added to give a precipitate. The precipitate was collected by filtration and loaded onto column chromatography with gradient elution of DCM/CH₃OH (0–10% CH₃OH). Evaporation of the solvent and trituration with diethyl ether afforded **2a** as a white solid (43 mg, 82% yield): *R_f* = 0.3–0.5 (4:1 dichloromethane to methanol); m.p. 135–137 °C; IR (CH₃OH solution) ν 3615, 2148, 1708, 1229, 658 cm^{–1}; ¹H NMR (400 MHz, CD₃OD) δ 8.00 (s, 1H), 7.85–7.79 (m, 2H), 7.41–7.37 (m, 1H), 7.02–6.98 (m, 1H), 6.93–6.79 (m, 4H), 5.36 (dd, *J* = 6.0, 8.5 Hz, 1H), 4.30 (s, 3H), 3.72 (dd, *J* = 5.7, 15.6 Hz, 1H), 3.53 (dd, *J* = 8.7, 15.6 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 170.2, 169.9, 160.1, 149.7, 147.8, 135.2, 130.1, 127.0, 126.2, 124.3, 123.9, 120.6, 120.5, 118.2, 117.2, 116.4,

53.0, 40.9, 30.8; HRMS (ESI) Anal. calcd. for $C_{20}H_{20}O_4N_3S^+$ m/z 398.1169 $[M-I]^+$, found 398.1164; $[\alpha]_D^{27} = -22.8$ (c 0.5, CH_3OH); HPLC analysis (CHIRALPAK IC (ϕ 0.46 cm $\times$ 25 cm), ethanol/*n*-hexane/trifluoroacetic acid/triethylamine = 20/80/0.5/0.5, flow rate 1.0 mL/min, detection at 290 nm, t_R = 14.6 min (major).

4.2.6. (S)-3-Benzyl-4-(2-(2-(benzyloxy)benzamido)-3-((2-(benzyloxy)phenyl)amino)-3-oxopropyl)thiazol-3-ium bromide 7b

The synthesis of **7b** was similar to the synthesis of **7a**. Compound **6** (113 mg, 0.2 mmol, 1 eq.) was dissolved in DMF (0.2 mL, 1 M) and 2 mL of benzyl bromide were used. The reaction mixture was stirred at room temperature till all **6** was consumed (typically 2 days). The same work-up procedure gave **7b** as a white solid (132 mg, 90% yield): R_f = 0.3–0.4 (7:1 dichloromethane to methanol); m.p. 103–105 °C; IR (CH_3OH solution) ν 3585, 3368, 1652, 1228, 825 cm^{-1} ; ^1H NMR (600 MHz, CD_3OD) δ 7.96 (dd, J = 1.4, 7.9 Hz, 1H), 7.82–7.80 (m, 2H), 7.53–7.50 (m, 1H), 7.43–7.39 (m, 5H), 7.35–7.32 (m, 4H), 7.21–7.18 (m, 4H), 7.15–7.11 (m, 4H), 7.07–7.05 (m, 2H), 6.96–6.94 (m, 1H), 5.78 (d, J = 15.1 Hz, 1H), 5.74 (d, J = 15.1 Hz, 1H), 5.22 (dd, J = 5.5, 8.6 Hz, 1H), 5.18 (d, J = 11.3 Hz, 1H), 5.10–5.04 (m, 3H), 3.53 (dd, J = 5.2, 15.8 Hz, 1H), 3.19 (dd, J = 8.6, 15.9 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 169.2, 168.2, 158.2, 150.5, 147.4, 137.9, 137.3, 134.8, 133.2, 132.2, 130.9, 130.8, 129.9, 129.8, 129.5, 129.2, 129.0, 128.5, 127.6, 126.7, 125.0, 123.4, 122.4,

122.3, 121.9, 114.6, 113.5, 72.1, 71.4, 57.7, 53.3, 30.6; HRMS (ESI) Anal. calcd. for $C_{40}H_{36}O_4N_3S^+$ m/z 654.2421 $[M-Br]^+$, found 654.2407; $[\alpha]_D^{27} = -0.9$ (c 1.0, CH_3OH).

4.2.7. (S)-3-Benzyl-4-(2-(2-hydroxybenzamido)-3-((2-hydroxyphenyl)amino)-3-oxopropyl)thiazol-3-ium bromide **2b**

The synthesis of **2b** was similar to the synthesis of **2a**. Compound **7b** (73 mg, 0.1 mmol, 1 eq.) was dissolved in dry DCM (1 mL), and cooled to $-78\text{ }^{\circ}\text{C}$ for 0.5 h. Next, BBr_3 (1 mL, 1 M in DCM, 1 mmol, 5 eq. relative to the Bn group) was added very slowly and stirred for another 0.5 h. The same work-up procedure gave **2b** as a white solid (41 mg, 75% yield): $R_f = 0.2\text{--}0.4$ (7:1 dichloromethane to methanol); m.p. $130\text{--}132\text{ }^{\circ}\text{C}$; IR (CH_3OH solution) ν 3542, 3368, 1707, 1646, 1229, 992, 762 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 9.90 (d, $J = 2.5\text{ Hz}$, 1H), 8.08 (d, $J = 2.5\text{ Hz}$, 1H), 7.85–7.81 (m, 2H), 7.48–7.37 (m, 6H), 7.01–6.97 (m, 1H), 6.93–6.90 (m, 2H), 6.86–6.79 (m, 2H), 5.94 (d, $J = 14.9\text{ Hz}$, 1H), 5.89 (d, $J = 15.1\text{ Hz}$, 1H), 5.29 (dd, $J = 6.0, 8.5\text{ Hz}$, 1H), 3.69 (dd, $J = 6.0, 15.8\text{ Hz}$, 1H), 3.48 (dd, $J = 8.5, 15.8\text{ Hz}$, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.2, 169.7, 160.7, 160.1, 149.6, 147.7, 135.3, 133.3, 130.9, 130.8, 130.2, 129.9, 127.0, 126.3, 125.5, 123.8, 120.6, 118.2, 117.2, 116.3, 57.9, 53.3, 31.0; HRMS (ESI) Anal. calcd. for $C_{26}H_{24}O_4N_3S^+$ m/z 474.1482 $[M-Br]^+$, found 474.1471; $[\alpha]_D^{27} = -26.4$ (c 0.7, CH_3OH); HPLC analysis (CHIRALPAK IC (ϕ 0.46 cm x 25 cm), ethanol/*n*-hexane/trifluoroacetic acid/triethylamine = 20/80/0.5/0.5,

flow rate 1.0 mL/min, detection at 290 nm, t_R = 14.1 min (major).

4.2.8. (S)-4-(2-(2-(Benzyloxy)benzamido)-3-((2-(benzyloxy)phenyl)amino)-3-oxopropyl)-3-(4-(decyloxy)benzyl)thiazol-3-ium bromide 7c

The synthesis of **7c** was similar to the synthesis of **7a**. Compound **6** (113 mg, 0.2 mmol, 1 eq.) was dissolved in DMF (0.2 mL, 1 M). The corresponding alkylation reagent (0.5 g) was used. The reaction mixture was stirred at room temperature until all of **6** was consumed (typically 2 days). The same work-up procedure gave **7c** as a white solid (164 mg, 92% yield): R_f = 0.4–0.6 (7:1 dichloromethane to methanol); m.p. 144–146 °C; IR (CH₃OH solution) ν 3402, 3022, 3014, 2361, 1710, 1601, 1514, 1363, 1210, 860 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 9.14 (s, 1H), 8.72 (d, J = 7.8 Hz, 1H), 7.99 (t, J = 8.0 Hz, 2H), 7.41–7.28 (m, 8H), 7.24–7.22 (m, 3H), 7.14–7.11 (m, 3H), 7.06–6.91 (m, 5H), 6.79 (d, J = 8.5 Hz, 2H), 5.88 (d, J = 14.7 Hz, 1H), 5.81 (d, J = 14.7 Hz, 1H), 5.30 (dd, J = 6.4, 14.0 Hz, 1H), 5.17 (d, J = 11.0 Hz, 1H), 5.05–5.03 (m, 3H), 3.84 (t, J = 6.4 Hz, 2H), 3.34 (dd, J = 6.0, 15.6 Hz, 1H), 3.22 (dd, J = 6.9, 15.6 Hz, 1H), 1.73–1.68 (m, 2H), 1.39–1.37 (m, 2H), 1.28–1.24 (m, 12H), 0.85 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 165.8, 160.0, 159.4, 156.8, 149.0, 146.0, 136.2, 135.4, 133.5, 131.9, 130.4, 128.8, 128.6, 128.5, 128.1, 128.0, 127.5, 126.6, 125.3, 123.1, 122.8, 122.2, 121.4, 121.1, 120.6, 115.3, 112.9, 112.1, 71.1, 70.6, 68.0, 56.6, 52.3, 31.8, 29.6, 29.5, 29.3, 29.2, 29.1, 25.9,

22.6, 14.1; HRMS (ESI) Anal. calcd. for $C_{50}H_{56}O_5N_3S^+$ m/z 810.3935 $[M-Br]^+$, found 810.3917; $[\alpha]_D^{27} = +0.5$ (c 0.5, $CHCl_3$).

**4.2.9. (S)-3-(4-(Decyloxy)benzyl)-4-(2-(2-hydroxybenzamido)-3-
-((2-hydroxyphenyl)amino)-3-oxopropyl)thiazol-3-ium bromide 2c**

Synthesis of **2c** was similar to the synthesis of **2a**. Compound **7c** (89 mg, 0.1 mmol, 1 eq.) was dissolved in dry DCM (1 mL), and cooled to $-78\text{ }^{\circ}\text{C}$ for 0.5 h. Next, BBr_3 (1 mL, 1 M in DCM, 1 mmol, 5 eq. relative to the Bn group) was added very slowly and stirred for another 0.5 h. The same work-up procedure gave **2c** as a white solid (55 mg, 78% yield): $R_f = 0.3\text{--}0.5$ (7:1 dichloromethane to methanol); m.p. $98\text{--}100\text{ }^{\circ}\text{C}$; IR (CH_3OH solution) ν 3117, 2928, 2856, 1710, 1640, 1603, 1514, 1362, 782 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.97 (s, 1H), 9.54 (d, $J = 2.4\text{ Hz}$, 1H), 8.48 (d, $J = 7.4\text{ Hz}$, 1H), 8.28 (s, 1H), 7.86 (d, $J = 2.8\text{ Hz}$, 1H), 7.81 (d, $J = 7.4\text{ Hz}$, 1H), 7.42–7.41 (m, 1H), 7.34–7.31 (m, 3H), 7.02–6.90 (m, 3H), 6.85–6.77 (m, 4H), 5.93 (d, $J = 14.7\text{ Hz}$, 1H), 5.85 (d, $J = 14.7\text{ Hz}$, 1H), 5.30 (dd, $J = 7.0, 14.4\text{ Hz}$, 1H), 3.89–3.79 (m, 3H), 3.62 (dd, $J = 7.4, 15.3\text{ Hz}$, 1H), 1.75–1.70 (m, 2H), 1.43–1.37 (m, 2H), 1.33–1.24 (m, 12H), 0.85 (t, $J = 6.7\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.8, 160.9, 160.3, 157.3, 149.0, 145.9, 134.8, 130.9, 127.5, 127.3, 124.5, 124.4, 124.0, 122.2, 120.4, 119.2, 118.2, 118.1, 115.6, 113.6, 68.2, 57.3, 52.0, 31.9, 30.2, 29.6, 29.4, 29.3, 29.1, 26.0, 22.6, 14.1; HRMS (ESI) Anal.

calcd. for $C_{36}H_{44}O_5N_3S^+$ m/z 630.2996 $[M-Br]^+$, found 630.2986; $[\alpha]_D^{27} = -17.8$ (c 0.5, $CHCl_3$); HPLC analysis (CHIRALPAK IC (ϕ 0.46 cm x 25 cm), ethanol/*n*-hexane/trifluoroacetic acid/triethylamine = 20/80/0.5/0.5, flow rate 1.0 mL/min, detection at 290 nm, t_R = 9.6 min (minor), 12.6 min (major).

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20. The prominent hydrogen binding interaction was observed for the catalytic system using **1**.
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22. After 48 h under otherwise identical conditions, **9f** was obtained with 40% ee.

Stereochemistry Abstract

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Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki* $C_{15}H_{18}O_4$ (<i>R</i>)-<i>tert</i>-Butyl 2-(4-oxochroman-3-yl)acetate	62% ee $[\alpha]_D^{27} = -2.3$ (c 1.8, CHCl₃) Absolute configuration: (<i>R</i>)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki* $C_{13}H_{14}O_4$ (<i>R</i>)-Ethyl 2-(4-oxochroman-3-yl)acetate	50% ee $[\alpha]_D^{27} = -2.5$ (c 1.7, CHCl₃) Absolute configuration: (<i>R</i>)

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Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki* $C_{16}H_{20}O_4$ (<i>R</i>)-<i>tert</i>-Butyl 2-(6-methyl-4-oxochroman-3-yl)acetate	63% ee $[\alpha]_D^{27} = -6.6$ (c 1.7, CHCl₃) Absolute configuration: (<i>R</i>)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

$C_{16}H_{20}O_5$

(*R*)-*tert*-Butyl 2-(6-methoxy-4-oxochroman-3-yl)acetate

59% ee

$[\alpha]_D^{27} = -12.7$ (c 2.3, $CHCl_3$)

Absolute configuration: (*R*)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

$C_{15}H_{17}ClO_4$

(*R*)-*tert*-Butyl 2-(6-chloro-4-oxochroman-3-yl)acetate

59% ee

$[\alpha]_D^{27} = -0.4$ (c 1.5, $CHCl_3$)

Absolute configuration: (*R*)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

$C_{18}H_{22}O_6$

(*R*)-Ethyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-4-oxochroman-6-carboxylate

55% ee

$[\alpha]_D^{27} = -5.6$ (c 1.9, $CHCl_3$)

Absolute configuration: (*R*)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

> 99% ee
 $[\alpha]_D^{27} = -6.6$ (c 0.7, CHCl₃)
 Absolute configuration: (S)

C₂₄H₂₇N₃O₄S

(S)-tert-Butyl (1-((2-(benzyloxy)phenyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-yl)carbamate

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

> 99% ee
 $[\alpha]_D^{27} = +48.7$ (c 0.5, CHCl₃)
 Absolute configuration: (S)

C₃₃H₂₉N₃O₄S

(S)-2-(Benzyloxy)-N-(1-((2-(benzyloxy)phenyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-yl)benzamide

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

> 99% ee
 $[\alpha]_D^{27} = -22.8$ (c 0.5, CH₃OH)
 Absolute configuration: (S)

C₂₀H₂₀IN₃O₄S

(S)-4-(2-(Hydroxybenzamido)-3-((2-hydroxyphenyl)amino)-3-oxopropyl)-3-methylthiazol-3-ium iodide

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

$C_{26}H_{24}BrN_3O_4S$ *(S)*-3-Benzyl-4-(2-(2-hydroxybenzamido)-3-((2-hydroxyphenyl)amino)-3-oxopropyl)thiazol-3-ium bromide

> 99% ee

 $[\alpha]_D^{27} = -26.4$ (*c* 0.7, CH₃OH)Absolute configuration: (*S*)

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

$C_{36}H_{44}BrN_3O_5S$ *(S)*-3-(4-(Decyloxy)benzyl)-4-(2-(2-hydroxybenzamido)-3-((2-hydroxyphenyl)amino)-3-oxopropyl)thiazol-3-ium bromide

> 99% ee

 $[\alpha]_D^{27} = -17.8$ (*c* 0.5, CHCl₃)Absolute configuration: (*S*)

Graphical Abstract